REMARKS

The claims have been amended to clarify the invention. Claims 1 and 2 have been amended to delete the recitation of differential expression in the claims. Claim 6 has been amended to replace the phrase "that disease" with "colon cancer". Claim 8 has been amended to delete the term "mimetics". Claim 9 has been amended to delete SEQ ID NOs:47 and 81, as well as a variant of SEQ ID NO:172 having at least 90% sequence identity to SEQ ID NO:172. No new matter is added by any of these amendments, and entry of the amendments is therefore requested.

Restriction Requirement

The Examiner stated that applicants election of Group I in Paper No. 9 is acknowledged. However, the Examiner stated, because applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse. MPEP § 818.03(a). In particular, the Examiner stated that applicants response did not address the aspects of the requirement for restriction between Groups I and VI, VII, and VIII, and so the election is being treated as an election without traverse. The Examiner also stated, however, that applicants' arguments in connection with the rejoining claims 4-12 with Group I, claims 1 and 3, is persuasive. Thus claims 4-12 are hereby rejoined with claims 1 and 3 to make Group I. Claims 1 and 3-12 are examined in this Office Action. The Examiner stated further that the combination examined includes the combinations containing each one of SEQ ID NOs:24, 47, 81, 104, 114, 165 and 172.

Applicants response

Applicants thank the Examiner for his reconsideration of the restriction requirement. However, applicants respectfully disagree that the election was not made with proper grounds for traverse. MPEP § 818.03(a) merely requires that the reasons on which the traverse is made cannot be a "mere broad allegation that the requirement is in error". See MPEP § 818.03(a), second paragraph. Clearly, the response to restriction requirement filed in Paper No. 9 gave specific reasons traversing the restriction requirement for Groups I-IV, and is therefore a proper election with traverse. There is no requirement in MPEP § 818.03(a) that "all aspects" of the restriction requirement must addressed for a proper election to be made with traverse.

35 U.S.C. § 112, Second Paragraph, Rejection of Claims 1 and 3-8

The Examiner has rejected claims 1 and 3-8 under 35 U.S.C. § 112, second paragraph, as

being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards ad the invention. The Examiner stated, in particular, that the claims are vague, indefinite, incomplete, misdescriptive and inaccurate:

(a) The recitation of "cDNAs that are differentially expressed" (claim 1) is inaccurate and misdescriptive because cDNAs are not expressed, but are artificial constructs.

(b) Claim 1 is vague and indefinite because it includes more combinations than the elected combinations.

(c) The recitation for "that disease" (claim 6) is incomplete because there is no antecedant basis for the term.

(d) The recitation of "specifically binding" (claim 7) is vague, indefinite, and incomplete because the term is a relative one and no frame of reference is given. The determination or characterization of specific binding requires knowledge or disclosure of other potential binding partners in the reaction mixture. None is given or mentioned

(e) The recitation of "specific binding" (claim 7) is vague, indefinite, and incomplete for the reasons given in (c) immediately above.

(f) the recitation of "mimetics" (claim 8) is vague and indefinite because it is not clear what is meant by the term.

Applicants Response

(a) Claim 1 has been amended to delete reference to "differential expression" in the preamble of the claim. The specification clearly describes cDNAs, as they are known in the art, to be stable constructs of actual expressed mRNAs, that are used in the described method for microarray analysis employed in present application. See, in particular, page 27, Example V, "Selection of Sequences, Microarray Preparation and Use"; and at pages 27-28, Example VI, "Preparation of Samples". Thus the specification clearly discloses that "differential expression" as the term is applied to the cDNAs of the invention, means the increased or decreased levels of detection of a cDNA in the microarray representing an expressed mRNA transcript.

(b) Claim 1 has been amended to recite a single combination of sequences which contains each one of SEQ ID NOs:24, 47, 81, 104, 114, 165 and 172, and therefore meets the Examiners

requirements for examination.

(c) Claim 6 has been amended to replace "that disease" with "colon cancer.

(d, e) Applicants disagree that the terms "specifically binding" and "specific binding" as recited in claim 7, are not clear and definite based on the disclosures in the specification and the common knowledge of one skilled in the art. "Specific Binding" is defined at page 9, lines 4-8 of the specification, which also includes pertinent examples of specific binding to DNA molecules . Methods to measure specific binding of the claimed polynucleotides to various ligands are described, and referenced, at page 13, line 29 through page 14, line 8, and again at Example XIV, page 34, lines 20-29 of the specification. In particular, a "high throughput" screening method, as recited in the preamble of the claim, is specifically referenced at page 34, lines 27-29 of the specification. Based on these disclosures, the skilled artisan would clearly be able to distinguish "specific" binding from "non-specific" binding in the recited method claim to achieve the intended result.

With these amendments and remarks, applicants submit that the claims are now clear and definite and request withdrawal of the rejection of claims 1 and 3-8 under 35 U.S.C. § 112, second paragraph.

35 U.S.C. § 101, Rejection of Claims 1 and 3-12

The Examiner has rejected claims 1 and 3-12 under 35 U.S.C. § 101, because the claimed invention lacks patentable utility. The Examiner stated that the application does not disclose a nexus between any particular or anticipated hybridization results to SEQ ID NOs:24, 47, 81, 104, 114, 165 and 172 and any disease state. The Examiner stated that the hybridization data shown in Table 1 and discussed on pages 9-10 of the instant application are not results of actual gene expression because they are disclosed as being cDNAs that hybridize to an array. Since cDNAs are artificial constructs, the Examiner alleges that they do not necessarily reflect levels of expression of genes. In addition, SEQ ID NO:47 (clone ID 1695477) is not expressed in polyp or tumor cells at half the level of normal cells a stated in the application in the paragraph bridging pages 9-10 (average downregulation according to Table 1 (page 2, line 19) is -1.07. The Examiner cited further data from Table 1 relative to SEQ ID NOs:102 and 114 alleging to show less than a two-fold differential expression in tumor vs normal tissue. The Examiner noted that no data is shown in Table 1 for SEQ ID NO:172 (clone ID 1846463) at all. Finally, the

Examiner stated, the application does not dislcose how the cDNA measurements were made.

Applicants Response

Applicants disagree that the specification does not clearly disclose how the microarray study represented by the results in Table 1 was conducted, and what these results mean in terms of a "nexus" with any disease state, in particular, colon cancer or colon polyps. As discussed previously in this response, the specification clearly acknowledges and discloses that the cDNAs of the invention are artificial, stable polynucleotide constructs representing actual mRNA transcripts. See, in particular, the specification at pages11-12 "cDNAs and Their Uses". Table 3 describes the specific probe sequences (Clone IDs) immobilized on a microarray and the full-length gene sequences (SEQ ID) from the Sequence Listing represented by the probe sequences. The specification describes, at pages 28-29 how total mRNA is prepared from clinical tissue samples and how complementary cDNA is prepared and labeled for detection in the microarray experiment. See ""Isolation and Labeling of Sample cDNAs". The specification then describes at page 29-30 how the hybridization reactions are carried out and the resulting hybridization complexes are detected and quantified. See "Hybridization and Detection". Finally, the specification at the bottom of page 30 discusses how the data was analyzed and the significance of the results. See "Data Analysis and Results". Of particular note is the disclosure that differential expression was considered significant only if at least a 2-fold difference was observed between two samples, and the fact that the data was presented as a log base 2 value (page 30, lines 28-29).

Thus clearly, in opposition to the Examiners' allegation, the specification fully describes the methods used in the microarray analysis and, in particular, how the cDNA measurements were made. The presentation of the results in Tables 1 and 2 on a log base 2 scale also explains the Examiners' misinterpretation of the results cited for specific SEQ ID NOs:47, 104, and 114 as

colon polyps or colon cancer compared with normal colon, as presented in Tables 1 and 2. Table 2 specifically lists, as disclosed in the specification at the bottom of page 5, Clone IDs representing genes not only differentially expressed in either colon polyps or colon cancer compared to normal colon, but also statistically more significantly expressed in colon cancer tissue than in colon polyps. Thus, SEQ ID NO:172 (Clone ID 1846463) is not present in Table 1, as the Examiner has observed, but is present in Table 2 as not only differentially expressed in both colon polyps and colon cancer relative to normal colon, but also more significantly expressed in colon cancer relative to colon polyps. Therefore, the data from Tables 1 and 2 clearly provide a "nexus" between the hybridization results for the claimed SEQ ID NOs: as representing genes differentially expressed in either colon cancer or colon polyps relative to normal colon.

The Examiners' unsupported allegation, presented at the bottom of page 3 of the Office Action, that "Since cDNAs are artificial constructs they do not necessarily reflect levels of expression of genes" is without merit. The Examiner offers no evidence or sound scientific reasoning why this statement would be generally accepted by the skilled artisan, particularly in view of the well-established use of cDNA microarrays in gene expression profiling dating back to as early as 1995. See attached declaration under 37 CFR 1.132 of Dr. John C. Rockett, discussed in more detail below. Furthermore, the Examiners' allegation does not specifically address why cDNA probes, constructed by well-established methods described at pages 28-29 of the specification to both qualitatively and quantitatively reflect expressed mRNAs in a tissue sample, would not be representative of expressed genes in the sample.

In addition, the Examiner has ignored a well-established utility for the claimed invention in gene expression profiling studies in toxicology that would be readily apparent to the skilled artisan at the time the instant application was filed. In support of this well-established utility, applicants have attached a declaration under 37 CFR 1.132 of Dr. John C. Rockett. The Rockett declaration describes, in particular, how the claimed polynucleotides can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing toxicological profiles for potential toxicants. Dr. Rockett states, for example, in ¶ 15, bottom of page 8 of the declaration that, with reference to well-characterized toxicants:

> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by such toxicants, this would appear a longer term goal, as the majority of human genes have not been sequenced, far less their functionality determined. However, the current use of gene profiling yields a *pattern* of gene changes for a xenobiotic of unknown toxicity which may be alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard ... (original emphasis).

Thus, the use of the claimed polynucleotides in gene expression profiling for potential toxicants represents a well established use independent of any functionality for the encoded polypeptide or known mechanism of toxicity for the encoded polypeptide.

For all of the above reasons, applicants submit that both specific and substantial, well-established and asserted utilities for the claimed invention are readily apparent from, and specifically disclosed in the specification and therefore request withdrawal of the rejection of claims 1 and 3-12 under 35 U.S.C. § 101.

35 U.S.C. § 112, First Paragraph, Rejection of Claims 1 and 3-12

The Examiner has rejected claims 1 and 3-12 under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The discussion in the rejection under 35 § 101 hereinabove is incorporated here. In addition, the Examiner stated, claim 1 is not enabled in its full breadth for reciting "differentially expressed in colon disorder" because the instant application does not enable diagnosis of any colon disorder.

Applicants Response

To the extent that the above rejection is based on an improper rejection of the same claims as lacking patentable utility for reasons discussed above in response to the rejection of claims under 35 U.S.C.§ 101, applicants submit that this rejection should similarly be withdrawn. Furthermore, claim 1 has been amended, as previously discussed, to delete reference to "any colon disorder". Withdrawal of the rejection is therefore requested.

35 U.S.C. § 102(b), Rejection of Claims 9-12

The Examiner has rejected claims 9-12 under 35 U.S.C § 102(b) as anticipated by either one of Hillman et al. (WO 99/41375, August 19, 1999) or Cao et al. (WO 98/38203, Sep. to be 2

application, and Gunn et al. discloses a cDNA that is 96.5% identical to SEQ ID NO:172. Both references disclose heterologous expression of the DNA.

Applicants Response

Claim 9 has been amended to delete SEQ ID NO:81 and a variant of SEQ ID NO:172 having at least 90% sequence identity to SEQ ID NO:172. Neither Hillman et al. nor Gunn et al. anticipate any of the other sequences recited in the claims, and withdrawal of the rejection of claims 9-12 under 35 U.S.C § 102(b) is therefore requested.

35 U.S.C. § 102(e), Rejection of Claims 9-12

The Examiner has rejected claims 9-12 under 35 U.S.C § 102(e) as anticipated by Bandman et al. (U.S. Patent No. 6,132,964). The Examiner stated that Bandman et al. discloses a cDNA (SEQ ID NO:13) that is 100% identical to SEQ ID NO:47 of the instant application. Bandman et al also teach the heterologous expression of the DNA.

Applicants Response

SEQ ID NO:47 has been deleted from the claims, and withdrawal of the rejection is therefore requested.

35 U.S.C. § 103(a), Rejection of Claims 9-12

The Examiner has also rejected claims 9-12 under 35 U.S.C. § 103(a) as being obvious over Bandman et al. (U.S. Patent No. 6,132,964). The applied reference has a common assignee with the instant application. The Examiner stated that based on the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). For applications filed on or after November 29, 1999, this rejection under 35 U.S.C. 103(a) might be overcome by a showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(I)(1) and § 706.02(I)(2).

Applicants Response

SEQ ID NO:47 has been deleted from the claims, and withdrawal of the rejection is therefore requested.

6,132,964. Although the conflicting claims are not identical, they are not patentably distinct from each other as SEQ ID NO:13 of U.S. Patent No. 6,132,964 is the same as SEQ ID NO:47 of the instant claims.

Applicants Response

SEQ ID NO:47 has been deleted from the claims, and withdrawal of the rejection is therefore requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections/rejections. Early notice to that effect is earnestly solicited. Applicants further request that upon allowance of claim 1, that claim 2 be rejoined and allowed as a subcombination of claim 1 containing allowable sequences in accordance with MPEP § 803.04.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE CORPORATION

Date: November 5, 2003

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LIST OF ATTACHMENTS: